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Shorter Survival in HIV-Positive Patients With Diarrhoea Who Excrete Adenovirus From the GI Tract

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Adenoviruses have been described as a cause of diarrhoea in patients infected with the human immunodeficiency virus (HIV). The prevalence of adenoviruses was studied in all HIV-positive patients presenting with diarrhoea at the Royal Free Hospital in London between 1991 and 1995. In addition, all postmortems carried out in HIV-positive individuals registered at the same centre between 1990 and 1997 were reviewed for evidence of adenovirus infection. Adenovirus was detected in 16.1% of patients presenting with diarrhoea. These individuals had a significantly lower CD4 count and were more likely to have had a diagnosis of acquired immunodeficiency syndrome (AIDS) than patients with diarrhoea in whom adenovirus was not detected. The median survival was 1 year compared with 2.4 years for those without adenoviruses; this difference remained significant (P = .008) after controlling for differences in CD4 counts between the groups. Gastrointestinal adenovirus excretion occurs at an advanced stage of HIV disease, and is associated with a poor prognosis. We suggest that adenoviruses may contribute to mortality in this population. ***J. Med. Virol. 58:280–285, 1999.***

KEY WORDS: enteric viruses; prognosis; clinical outcome; postmortem

INTRODUCTION

Adenoviruses are double-stranded DNA viruses that have been associated with the development of upper respiratory tract infections, gastroenteritis, conjunctivitis, and haemorrhagic cystitis in immunocompetent individuals [Khoo et al., 1995]. Prevalence rates of adenovirus among human immunodeficiency virus (HIV)-infected patients range from 0% to 29% [Kotler et al., 1984; Laughon et al., 1988; Kaljot et al., 1989; Janoff et al., 1991; Thea et al., 1993; Khoo et al., 1995]. The most commonly recognised manifestation of adenovirus infection in HIV disease is diarrhoea [Cunningham et al., 1988; Kaljot et al., 1989; Grohmann et al., 1993; Thea et al., 1993]. Other clinical associations with adenovirus in HIV-infected patients include pneumonitis [Valainis et al., 1989], meningoencephalitis [West et al., 1985; Schnurr et al., 1995], hepatitis [Krilov et al., 1990], colitis [Janoff et al., 1991; Maddox et al., 1992], neuronal degeneration [Horoupian et al., 1984], urinary tract infection [Shintaku et al., 1993; Green et al., 1994], myositis [Khoo et al., 1995], and parotitis [Gelfand et al., 1994]. It has been suggested that adenovirus infection is often severe and may be associated with significant morbidity and mortality. Indeed, in one study, it was reported that 45% of acquired immunodeficiency syndrome (AIDS) patients infected with adenovirus died within 2 months of virus detection [Hierholzer, 1992]. However, it is not clear whether this poor survival is due to adenovirus infection itself, or simply reflects the severely immunocompromised nature of these individuals at the time of presentation.

The aims of this study were first to assess the prevalence of adenovirus infection in HIV-positive patients presenting with diarrhoea at a major HIV treatment centre in the United Kingdom. The second aim was to assess the clinical and prognostic significance of confirmed adenovirus infection for subsequent survival in these patients, taking account of other prognostic markers such as the CD4 count and disease stage. Fi-

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TABLE I. Prevalence of Adenovirus Infection in Faeces From HIV-Positive Patients With Diarrhoea

Year	No. cultures	Isolates adenovirus-positive		No. patients	Patients adenovirus-positive	
		No.	(%)		No.	(%)
1991	182	34	18.7	70	14	20.0
1992	217	41	18.9	69	14	20.3
1993	180	22	12.2	57	6	10.5
1994	191	26	13.6	64	10	15.6
1995	86	8	9.3	45	5	11.1
Total	856	131	15.3	305	49	16.1

nally, multiple tissues were collected from 62 postmortems to determine if disseminated infection was present.

PATIENTS AND METHODS

Clinical Study

All stool samples from individuals with diarrhoea sent to the Royal Free Hospital (RFH) Virology department between 1991 and 1995 were inoculated into cell cultures susceptible to several viruses, including adenoviruses. Samples were also submitted for standard bacteriological and parasitological investigation. Individuals with samples in which adenovirus was detected were defined as cases; all other patients with samples in which adenovirus was not detected were used as controls. Clinical follow-up of patients was complete to the end of 1996; cases were followed for a maximum of 4.60 years (median 0.86 years) and controls for 5.91 years (median 1.58 years). Details of clinical staging, CD4 count, and medical history for all individuals were obtained from a clinical database stored at the hospital. Data were not available on the severity of diarrhoea in cases or controls.

Postmortem Study

Between 1990 and 1997, adenovirus infection was specifically sought using cell cultures in the following tissues from all 62 postmortem cases carried out on HIV-positive individuals at the Royal Free Hospital: lymph node, brain, spinal cord, vitreous humour, optic nerve, skin, salivary gland, thyroid, trachea, lung, heart, oesophagus, stomach, duodenum, colon, liver, spleen, pancreas, kidney, adrenal gland, prostate, dorsal root ganglion, bladder, and small bowel.

Laboratory Methods

Stool cultures. Stool samples (approximately 1 g) emulsified in 5 ml of viral transport media were frozen at –70°C for 1 hr and then thawed at 37°C before being centrifuged at 3,000 rpm for 10 min. The resulting supernatants were inoculated into two tubes containing human embryonic lung cell monolayers, and two tubes containing rhesus monkey kidney cell monolayers. The tubes were incubated stationary at 37°C for 1 hr before being re-fed with fresh maintenance medium. The tubes were incubated stationary at 37°C and examined microscopically at intervals for up to 21 days for the development of a characteristic cytopathic effect (CPE). Positive cultures were confirmed by electron microscopy.

Postmortem tissue cultures. Approximately 1 g of sample collected at postmortem was homogenised in viral transport medium, inoculated into cell culture tubes, and examined as above. Positive cultures were confirmed by electron microscopy.

Statistical Methods

The demographic and clinical features of the cases and controls at baseline were compared using chi-squared tests, Fisher's exact tests and Mann–Whitney *U* tests, where appropriate. Standard survival methods were used to compare survival rates following first presentation with diarrhoea in cases and controls. For patients in whom adenovirus was detected in more than one stool sample, the date of the first positive sample was used as baseline. For patients who remained alive and under clinical follow-up at the end of the study period (31 December 1996), follow-up was right-censored on 31 December 1996. For patients who were not currently under follow-up, but who were alive when last seen, follow-up was right-censored on the date of their last visit to the hospital. Kaplan–Meier plots were used to display survival visually in cases and controls; differences in these survival plots were tested for significance using the log-rank test [Cox and Oakes, 1984]. To quantify these relationships, and to adjust for other prognostic markers at baseline, Cox proportional hazards models were used [Cox and Oakes, 1984]. All factors were included as fixed covariates at baseline. In a further analysis, progression to AIDS in those patients who had not had an AIDS diagnosis at the time of diarrhoea, was considered in a similar way. All analyses were carried out using the LIFETEST and PHREG procedures in the Statistical Analysis System [SAS Institute Inc., 1989].

RESULTS

The prevalence of adenovirus in faecal samples from all patients with diarrhoea is shown in Table I. Of a total of 856 cultures, 131 (15%) were positive for adenovirus. Forty-nine of 305 patients had at least one positive culture over the time period (16%, 95% confidence interval [CI] 12–20%); these individuals are included in the study as cases. Of these, 50% had only one isolate that was positive for adenovirus, 20% had two positive isolates, and the remaining 30% had more

TABLE II. Demographic Details of Cases and Controls Included in Study

Characteristic	No. of patients: Cases (n = 49)	No. of patients: Controls (n = 256)	P
Sex			
Male	44 (89.8%)	232 (90.6%)	
Female	5 (10.2%)	24 (9.4%)	.79
Risk group			
Homosexual	42 (85.7%)	197 (77.0%)	
Other	7 (14.3%)	59 (23.1%)	.24
Age at time of sample (years)	35 (24–55)	34 (19–66)	.23
CD4 count at time of sample (cells/mm^3)	20 (0–400)	90 (0–1332)	.0001
Number (%) with previous AIDS diagnosis	40 (81.6%)	133 (52.0%)	.001
Number (%) deaths	44 (89.9%)	132 (51.6%)	.001

than two positive isolates (maximum 13). All 256 individuals presenting at the hospital with diarrhoea in whom adenovirus was not detected were included in the study as controls. There was no statistical difference in the proportion of cases and controls according to the year of presentation (P = .44, Fisher's exact test).

Demographic and clinical characteristics of cases and controls are shown in Table II. Most patients included in the study were male homosexuals with a median age of 34 years at presentation. There were no significant differences between cases and controls in risk group, sex, or age at presentation. However, cases had significantly lower CD4 counts at the time of diagnosis than controls (P = .0001, Mann–Whitney U test) and were more likely to have a previous diagnosis of AIDS (P = .001, Chi-squared test). Throughout follow-up a significantly higher proportion of cases (89.8%) died compared with controls (51.6%, P = .001, Chi-squared test).

One case and one control patient died within a day of presenting with diarrhoea and have not been included in the follow-up analysis. Follow-up information is unavailable on a further 6 control patients who did not re-attend the centre following their presentation with diarrhoea. Hence, the follow-up analysis is based on 48 case and 249 control patients. These individuals had median survival times of 0.97 years and 2.43 years, respectively (P = .0001, log-rank test, Fig. 1). In univariate Cox regression analyses, cases were more likely to die during follow-up than controls (Table III). However, as the baseline CD4 count of the individuals, year of presentation, and a previous AIDS diagnosis were all significantly associated with survival in univariate analyses, these factors were included in a multivariate model to identify whether the adenovirus status of the individual was independently associated with survival. After adjusting for baseline CD4 count, year of presentation and whether patients had a previous AIDS diagnosis, cases remained at a significantly higher risk of death than controls (relative hazard 1.64, Table III).

Follow-up information was available for 9 cases and 118 controls who were initially AIDS-free at the time of presentation with diarrhoea. Over follow-up, 8 of the cases and 52 of the controls developed AIDS with median progression times of 1.43 years and 3.29 years, respectively (P = .009, log-rank test). Cox proportional hazards regression analyses revealed that in univariate analyses, the hazard of developing AIDS in cases was higher than that in controls. However, after adjusting for CD4 count and year of presentation, this effect, although still raised (relative hazard 1.67), became nonsignificant (Table III).

Of the 49 cases, 24 (49.0%) had samples in which adenovirus was detected on more than one occasion. There were no differences between cases in whom adenovirus was detected on more than one occasion and those in whom it was detected on one occasion only in terms of baseline CD4 count or age (P = .60 and .15 respectively, Mann–Whitney U test). Further, although the numbers were small, there was no evidence of any survival difference between the two groups, (P = .95, log-rank test).

Postmortem Study

Of the 62 individuals investigated at postmortem, adenovirus was cultured from 5 patients from at least one site (8%, 95% confidence interval 3–18%, Table IV). Three of these patients had stool cultures that were positive for adenovirus when alive, the other two had negative stool cultures when alive. Of the 57 individuals in whom adenovirus was not cultured at postmortem, 4 had previously had positive stool cultures. A summary of the clinical findings from postmortem is reported in Table V.

DISCUSSION

Adenovirus was detected in 16% of patients presenting with diarrhoea at our treatment centre over a 5-year period. No association was found between detection of adenovirus and other reported clinical manifestations of infection. This is almost certainly due to the fact that only those patients presenting with diarrhoea were screened for the presence of adenovirus. These patients were at a very advanced stage of HIV disease, as indicated by very low CD4 counts, and had a high rate of prior AIDS diagnoses. However, even after taking this into account, patients in whom adenovirus was detected had a worse prognosis than control patients with diarrhoea in whom adenovirus was not detected.

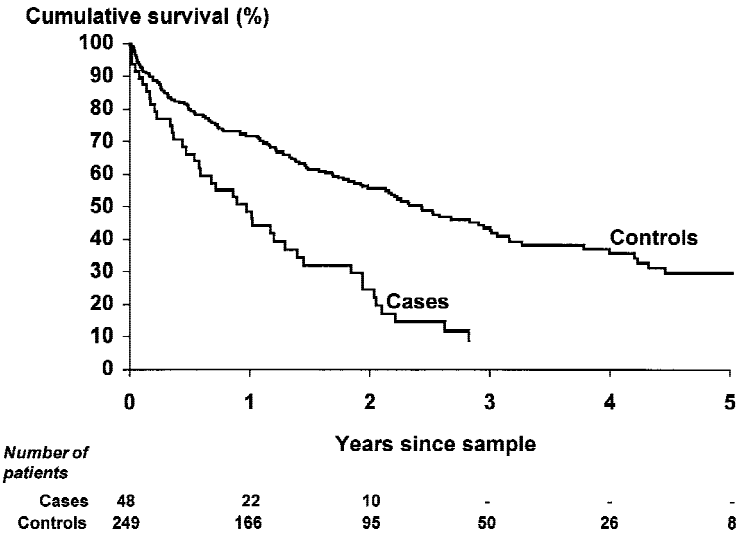

Fig. 1. Kaplan–Meier plot showing cumulative survival following presentation with diarrhoea according to adenovirus status.

TABLE III. Relative Hazards (and 95% Confidence Intervals [CI]) of Death and Developing AIDS Associated With Adenovirus Positivity, Unadjusted and After Adjustment for CD4 Count, Year of Sample, and Previous AIDS Diagnosis

	Death	AIDS
Unadjusted		
Relative hazard	2.53	2.62
95% CI	(1.79–3.59)	(1.24–5.54)
P	0.0001	0.01
Adjusted		
Relative hazard	1.64	1.67
95% CI	(1.14–2.36)	(0.78–3.56)
P	0.008	0.19

TABLE IV. Organs Sampled at Autopsy That Contained Detectable Adenoviruses

	Patient no.				
Body site	1	2	3	4	5
Trachea	+	–	–	–	–
Lung	+	+	–	–	–
Salivary gland	+	–	–	–	–
Pancreas	+	–	–	–	–
Spleen	+	–	–	–	–
Oesophagus	+	+	–	–	+
Thyroid	+	+	–	–	–
Kidney	+	–	–	–	–
Lymph node	+	–	–	–	–
Liver	–	+	+	–	–
Colon	–	+	–	+	+
Heart	–	+	–	–	–
Duodenum	–	–	–	–	+

All other sites cultured were negative in all five individuals.

At postmortem, adenovirus was detected in 5 of 62 cases, indicating that even in the absence of symptoms relating to specific organs, adenovirus may be detectable in a small proportion of individuals.

Infection with adenovirus is thought to be more common in individuals infected with HIV than in HIV-negative controls [Durepaire et al., 1995; Crawford-Miksza and Schnurr, 1996]. In HIV-positive patients, prevalence rates range from 0% to 29% [Kotler et al., 1984; Laughon et al., 1988; Kaljot et al., 1989; Janoff et al., 1991; Thea et al., 1993; Khoo et al., 1995]. However, at later stages of disease, rates are higher [Cunningham et al., 1988; Durepaire et al., 1995] with a 1-year risk of infection of 31–38% [Khoo et al., 1995]. Diarrhoea is a relatively common complaint in HIV-positive individuals, with a reported incidence rate of 11% per month [Grohmann et al., 1993]. Whilst adenovirus has been implicated as a major cause of symptoms in these individuals, not all studies find a strong association between diarrhoea and adenovirus infection [Cunningham et al., 1988; Laughon et al., 1988; Kaljot et al., 1989; Janoff et al., 1991; Grohmann et al., 1993; Thea et al., 1993; Durepaire et al., 1995]. However, the CPE of adenoviruses can resemble that of cytomegalovirus (CMV), so it is possible that some cases of adenovirus have been misdiagnosed in the past. We find that electron microscopy is a simple and rapid way of distinguishing between these CPEs. The reported rate of 16% in our study is therefore consistent with findings in these studies. The differences between the studies may be related to the different detection methods used or background prevalence rates in the countries and risk groups studied.

The prognostic role of adenovirus is unclear. In one study, it was reported that 45% of AIDS patients with adenovirus died within 2 years of detection [Hierholzer, 1992]. However, these results may be biased with only those individuals who present with severe forms of diarrhoea being investigated for the presence of viral pathogens. In other studies, it has been reported that adenovirus may often be associated with asymptomatic infection, and that the poor prognosis in some individuals simply reflects the advanced immunosuppression of these individuals at the time of presentation [Durepaire et al., 1995]. The finding of an association be-

TABLE V. Clinical Features and Postmortem Findings in Patients Undergoing Autopsy

	Patient no.				
	1	2	3	4	5
Sex	M	M	M	F	M
Age (years)	35	31	42	23	33
Sexual orientation	Homosexual	Homosexual	Bisexual	Heterosexual	Homosexual
AIDS-defining diagnoses	Cytomegalovirus pneumonitis and oesophagitis Kaposi's sarcoma (cutaneous and pulmonary)	PCP	Cerebral toxoplasmosis	Pulmonary tuberculosis	PCP Cerebral toxoplasmosis Kaposi's sarcoma (cutaneous and pulmonary) Oesophageal Candida Recurrent bacterial pneumonia
Non-AIDS-defining conditions	Calculus cholecystitis Shingles Abnormal liver function	Neutropenic sepsis Bronchiectasis Abnormal liver function	Psoriasis Anaemia and thrombocytopenia Abnormal liver function	HIV nephropathy	
Postmortem findings	Bilateral pneumonia Meningoencephalitis Hepatosplenomegaly Vacuolar myelopathy	Bilateral adenovirus pneumonitis Hepatic infarct Diffuse polio-dystrophy	Bilateral pneumonia Cerebral oedema	Bilateral pneumonia Splenomegaly	Bilateral pneumonia HIV encephalopathy Hepatosplenomegaly

PCP, *Pneumocystis carinii* pneumonia.

tween the presence of adenovirus and CD4 count was not surprising, given the earlier findings from both Cunningham et al. [1988] and Durepaire et al. [1995], noting an association between disease stage and adenovirus detection. However, what was striking was the degree of immunosuppression of the patients in this study in whom adenovirus was detected. Median CD4 counts in this group were only 20 cells/mm^3. Thus it would be expected that individuals in this group would have a very poor prognosis. Our findings show that whilst some of the difference in progression rates can be explained by the low CD4 counts in this group, there remains a significant additional poor prognosis associated with the detection of adenovirus.

It should be noted that not all adenoviruses grow in cell culture; in particular types 40 and 41. Our results therefore focus on those adenoviruses able to cause systemic infection, and may lead to an underestimate of the impact of adenovirus in our patients. Furthermore, many patients were sampled on only one occasion so providing a further underestimate of the potential impact of adenovirus infection. This possibly explains why two patients had adenovirus detected at autopsy but not antemortem, and further studies with closer sampling are clearly required.

There are a number of limitations to our study that should be considered. First, we have only studied individuals who presented to the Royal Free Hospital with diarrhoea and therefore have no data on prevalence rates in individuals without diarrhoea or in those with mild diarrhoea who chose not to report to our centre. Thus, our findings about poor prognosis are limited to those in whom diarrhoea was present and sufficiently severe or prolonged to require attendance at a treatment centre. Second, we have no information on other potential causes of diarrhoea in these patients. It is possible that the cases and controls in our study were infected with any of a number of other pathogens. Thus, the possibility cannot be excluded that poor prognosis in these individuals was due to infection with a different pathogen that may be associated with adenovirus infection. Thirdly, adenovirus was not subtyped in this study due to the lack of a full range of anti-sera. Forty-nine subtypes have been identified to date and seroepidemiological studies show that certain subtypes are found more commonly in HIV-infected individuals [Crawford-Miksza and Schnurr, 1996]. Although the precise role of these subtypes is unclear, it is possible that some may be more pathogenic than others. Finally, as many of these individuals presented before the routine introduction of HIV viral load testing, we do not have any information on HIV-1 RNA levels in these patients.

Adenovirus was found in 5 of 62 postmortem cases (8.1%). The medical history prior to death of these individuals was similar to that seen in the remaining 57 postmortem cases. There were no particular premortem clinical features identified that distinguished those in whom adenovirus was subsequently detected. All postmortem examinations revealed multiple pathologies and in only one case (patient 2) was it thought that adenovirus was a significant cause of pathology at death. Thus, the most likely explanation for our findings is that adenoviruses act as opportunistic infec-

tions contributing to the multisystemic symptoms experienced by AIDS patients without producing clinical signs, as illustrated by the complex range of infection and other conditions found at autopsy.

In conclusion, we report high rates of adenovirus in patients with diarrhoea at our centre. Even allowing for the fact that individuals with adenovirus are at more advanced stages of HIV infection, with very low CD4 counts, adenovirus remains associated with shorter survival, and we suggest that the virus may contribute to mortality in this population.

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